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Pharmacokinetics and Renal Tolerance of Aztreonam in Premature Infants

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Aztreonam (30 mg/kg of body weight) was administered intravenously over 3 min every 12 h to 30 preterm neonates divided into two groups according to gestational age (mean age for group A was <30 weeks and mean age for group B was >30 weeks) and birth weight (mean weight for group A was <1,500 g and mean weight for group B was >1,500 g). Blood and urine samples were analyzed by microbiological assay. The pharmacokinetics were described by one-compartment and noncompartment models. The mean half-life and clearance for premature infants weighing less than 1,500 g were 5.33 ± 3.61 h and 1.52 ± 1.33 ml/min/kg, respectively; for those weighing more than 1,500 g, the values were 4.08 ± 2.28 h and 2.41 ± 2.10 ml/min/kg, respectively. The mean urinary concentration of aztreonam in 15 premature infants during the first 6 h of therapy was 242.72 ± 188.19 μg/ml, with a mean percentage of elimination of 13.29%. Urinary excretion of *N*-acetyl-β-D-glucosaminidase (a specific and sensitive test for the detection of drug-induced renal tubule damage) did not show significant differences in our group of premature infants compared with that in a control group. The dose of 30 mg/kg and a dosage interval of 8 to 12 h could be recommended for the treatment of suitable bacterial infections in all premature infants.

Aztreonam is a monobactam compound that shows excellent activity against aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* (10).

Preterm infants, being of low birth weight and often requiring prolonged positive-pressure ventilation and parenteral nutrition, are highly susceptible to infections. Because potentially serious infections require urgent treatment before bacteriological test results are available, babies treated in the first 48 h of life often receive antibiotics when the risk of infection exists but before clinical signs develop, such as following prolonged rupture of the membranes. In this situation, antibiotics must be effective against the whole spectrum of pathogens (6). Combined with ampicillin, aztreonam could be an ideal antimicrobial agent for initial empiric therapy of sepsis neonatorum, because of its aminoglycosidelike antibacterial activity and the lack of the ototoxicity and nephrotoxicity that occasionally occur in aminoglycoside-treated neonates (2). Here we report and correlate plasma aztreonam concentrations with its pharmacokinetic profile and renal tolerance in low-birth-weight premature infants with suspected serious infections within the first 48 h after birth.

MATERIALS AND METHODS

Study patients. Our study population comprised 30 premature infants hospitalized in the Neonatal Intensive Care Unit, Department of Paediatrics, Verona University, with suspected or proven bacterial infections. After informed, written consent was obtained from the parents, aztreonam was given with ampicillin (100 mg/kg of body weight per day); if bacteriology was positive or infection was clinically present although not confirmed, the premature infants received a full course of antibiotic (mean duration of treatment, 7 days). Routine laboratory tests, hematology, biochemistry, and urinalysis were carried out during treatment to assess the systemic tolerance of the drug.

Drug administration and sampling for drug assay. Aztreonam was given in intravenous doses of 30 mg/kg over 3 min every 12 h. Blood samples were collected at the following times after the first dose of aztreonam, which was given alone: 1, 2, 3, 4.5, 6, and 8 h (no more than four specimens were collected from each premature infant). Urine samples were collected during the first 6 h of therapy and analyzed for the recovery of aztreonam in urine. Additional urine samples were obtained after 1, 3, 4, 7, and 11 days from the beginning of therapy for *N*-acetyl-β-D-glucosaminidase (NAG) detection.

Aztreonam assay. Concentrations of aztreonam in plasma and urine were measured by an agar disk diffusion technique, with an ampicillin-resistant *Escherichia coli* strain used as the test organism (5). Urine samples were diluted 1:10 with a 1% phosphate buffer (pH 6). The coefficient of variation for aztreonam was 5%.

NAG enzymuria (a specific and sensitive test for the detection of drug-induced renal tubule damage) was assayed by a colorimetric test by a standard procedure described in a previous study (3) in treated and control groups.

Pharmacokinetic analysis. Data on the concentration of aztreonam in serum were analyzed by moment analysis (1). The elimination rate constant β was derived from fitting a one-exponent equation to the serum concentration-time data, since values for only three or four serum samples were determined for each patient. The elimination half-life ($t_{1/2\beta}$) was calculated as $t_{1/2}=\ln 2/\beta$; the clearance from serum (CL_S) was calculated as dose/AUC, where AUC is area under the plasma drug concentration-time curve. The AUC and the area under the first moment of the drug concentration-time curve were calculated by the trapezoidal rule method with

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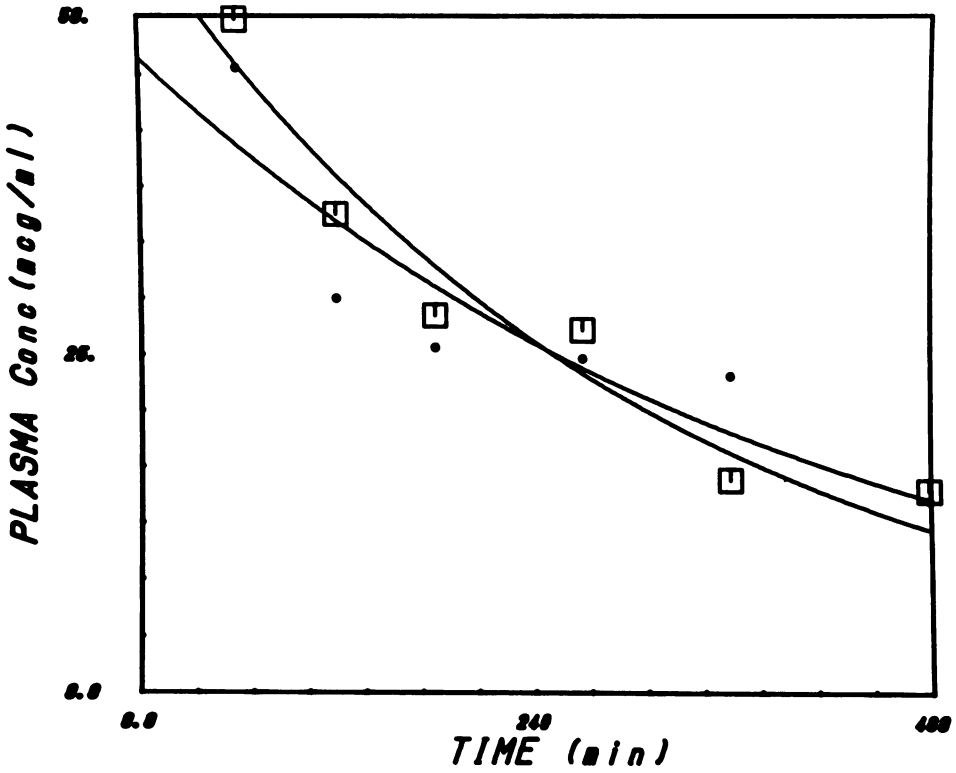

FIG. 1. Mean plasma concentration-time curve after the first dose of aztreonam in premature infants in groups A (●) and B (□). Values are expressed as means ± standard deviations.

extrapolation to infinity (1). The volume of distribution at steady-state was calculated as MRT · CL_S, where MRT is mean residence time.

Statistical evaluation. Differences among our groups were analyzed by using the Student *t* test.

RESULTS

Patient characteristics. The 30 premature infants enrolled in this study were divided into two groups according to gestational age and birth weight. Group A was made up of 14 premature infants with a mean gestational age of 27.6 ± 2.03 weeks (standard deviation) and a mean birth weight of 1,060.7 ± 331.67 g. Group B was made up of 16 infants with a mean gestational age of 32.4 ± 1.93 weeks and a mean birth weight of 1,639.6 ± 392.87 g.

Concentrations in plasma. The mean concentrations of aztreonam in plasma for both groups of premature infants are shown in Fig. 1. At 1 h from the time of drug administration, the mean values were 46.33 and 49.72 μg/ml for groups A and B, respectively; after 8 h the mean values were similar (14.10 versus 14.83).

Concentrations in urine. The concentrations of aztreonam in the urine of 15 premature infants during the first 6 h of therapy were from 58.7 to 510 μg/ml, with a mean ± standard deviation of 242.72 ± 188.19 μg/ml; the mean percent elimination of the drug was 13.29%. There were no significant differences for the concentrations of aztreonam in urine among the two groups, even if a large variability in drug elimination was evident.

Urinary excretion of NAG in our groups compared with that in a control group is shown in Table 1. There were no statistically significant differences among the three groups.

Pharmacokinetic profile. The aztreonam kinetic parameters are given in Table 2. Pharmacokinetic values did not show significant differences among the two groups, even if the $t_{1/2}$ and CL values in plasma were somewhat different: 5.33 h and 1.52 ml/min/kg, respectively, for group A and 4.08 h and 2.41 ml/min/kg, respectively, for group B.

Safety and tolerance. The intravenous infusion of aztreonam was well tolerated, without any apparent clinical or laboratory adverse effects.

DISCUSSION

In this study, the mean plasma $t_{1/2}$ ranged from 4.08 to 5.33 h and the systemic CL ranged from 1.52 to 2.41 ml/min/kg. These values are not comparable to those observed previously in low-birth-weight infants (2). The average volume of distribution observed in the present study was high, corresponding to the high extracellular water content in premature infants. Moreover, the slow renal elimination of the

TABLE 1. Urinary excretion of NAG in a control group (22 preterm neonates) and in the two groups treated with aztreonam

Day	Urinary excretion (mU/min) of NAG in[a]:		
	Control group (n = 22)	Group A (n = 14)	Group B (n = 16)
1	0.67 ± 0.47	0.75 ± 0.46	0.71 ± 0.39
3	0.63 ± 0.44	0.86 ± 0.63	0.82 ± 0.58
4	0.50 ± 0.55	0.49 ± 0.44	0.48 ± 0.42
7	0.33 ± 0.34	0.32 ± 0.25	0.31 ± 0.26
11		0.34 ± 0.22	0.32 ± 0.19

[a] Values are means ± standard deviations.

TABLE 2. Aztreonam pharmacokinetic parameters in preterm neonates[a]

Group	β (h^{-1})	$t_{1/2\beta}$ (h)	AUC (μg · h/ml)	V_{SS} (ml/kg)	CL_S (ml/min/kg)	AUMC (μg · h^2/ml)	MRT (h)
A	0.13 ± 0.07	5.33 ± 3.61	340.35 ± 152.84	639.3 ± 421.3	1.52 ± 1.33	2,385.9 ± 1,291.6	7.01 ± 3.09
B	0.17 ± 0.09	4.08 ± 2.28	323.92 ± 105.80	1,012.2 ± 578.2	2.41 ± 2.10	2,524.6 ± 1,542.3	7.79 ± 3.25

[a] Values are means ± standard deviations. β, elimination rate constant, $t_{1/2\beta}$, elimination half-life; AUC, area under the plasma drug concentration-time curve; V_{SS}, volume of distribution at steady state; CL_S, clearance from serum; AUMC, area under the first moment of the drug concentration-time curve; MRT, mean residence time.

drug, despite a more rapid clearance from the plasma, may take into account the high volume of distribution of aztreonam, since it is known to be a minor route of extrarenal elimination or metabolism of this drug (8). Besides differences in the assay method for aztreonam and in the analysis of data from previous investigations (9), which were based on the determination of numerous plasma aztreonam levels, differences in the severity of the illness, gestational age, and time of drug administration must also be considered in evaluating the difference between some pharmacokinetic parameters. The elimination kinetics of aztreonam do not indicate any tendency for the drug to accumulate in these preterm infants, even if the mean residence time is about 7 h. These pharmacokinetic properties suggest that a dosage interval of 8 to 12 h in our patients would be appropriate for initial multiple-dose clinical trials (7). Moreover, in our premature infants, the 30-mg/kg intravenous dose produced concentrations in plasma that widely exceeded the MIC for 90% of the aerobic gram-negative bacteria, including *Pseudomonas aeruginosa* (10), in both groups of infants at 8 h. Although the concentrations of aztreonam in urine varied considerably, the lowest levels obtained during the first 6 h exceeded the MIC for 90% of aerobic gram-negative bacteria. In addition, aztreonam appeared to have a low potential for renal injury, because levels of NAG in urine of premature infants were similar to those in urine of controls. Since this enzyme, whose increase is dependent on drug dosage (4), was not modified in our study, it further confirms that aztreonam does not accumulate in plasma or renal tissue.

This fact confirms the good renal tolerance of aztreonam and suggests that this antibiotic, in combination with ampicillin, could be effective for initial therapy of neonatal sepsis in low-birth-weight infants, whose renal function is physiologically reduced.

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